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SEQUENTIAL HIGH THROUGHPUT SCREENING METHOD AND SYSTEM

BACKGROUND

1. Field of the Invention:

The present invention relates to a sequential high throughput screening (HTS) method and system.

2. Discussion of Related Art:

In experimental reaction systems, each potential combination of reactant, catalyst and condition should be evaluated in a manner that provides correlation to performance in a production scale reactor. Combinatorial organic synthesis (COS) is an HTS methodology that was developed for pharmaceuticals. COS uses systematic and repetitive synthesis to produce diverse molecular entities formed from sets of chemical "building blocks." As with traditional research, COS relies on experimental synthesis methodology. However instead of synthesizing a single compound, COS exploits automation and miniaturization to produce large libraries of compounds through successive stages, each of which produces a chemical modification of an existing molecule of a preceding stage. The procedure provides large libraries of diverse compounds that can be screened for various activities.

The techniques used to prepare such libraries involve a stepwise or sequential coupling of building blocks to form the compounds of interest. For example, Pirrung *et al.*, U.S. Pat. 5,143,854 ostensibly discloses a technique for generating arrays of peptides and other molecules using, for example, light-directed, spatially-addressable synthesis techniques. Pirrung synthesized polypeptide arrays on a substrate by attaching photoremovable groups to the surface of the substrate, exposing selected regions of the substrate to light to activate those regions, attaching an amino acid monomer with a photoremovable group to the activated region, and repeating the steps of activation and attachment until polypeptides of the desired length and sequences are synthesized.

According to the teachings of Pirrung, each synthesis requires bringing the array to reaction conditions, which requires time. If multiple synthesis steps are utilized as is often the case, each synthesis step should be carefully controlled to achieve uniform reaction conditions and time. Uniform reaction conditions and time periods are difficult to achieve with batch processing of array plates. Further, it is difficult to define and control reaction time with batch processing, since each array plate must be individually "ramped" to target synthesis conditions and then "backed off" from the conditions upon completing the reaction. Considerable manual manipulation may be required at startup and shutdown in adjusting controls, loading samples and bolting enclosures.

Additionally, a high pressure reactor large enough to hold an array plate would require thick walls that cause a delay in controlling temperature. Adjustment of temperature within the reactor always lags behind adjustment at the temperature control. This can be a serious problem where precise temperature control is required. For example, catalyst reaction studies typically require temperature measurement and control to better than ±2°C (preferably ±0.5°C).

There is a need for an HTS method and system to easily conduct multiple syntheses under identical or precisely controlled variable conditions and reaction times.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to a method and apparatus for rapid screening of multiphase reactant systems. In one exemplary embodiment, the method includes the steps of sequentially loading a plurality of discrete combinations of reactants into a longitudinal reaction zone; reacting each of the combinations as it passes through the reaction zone to provide a continuously or an incrementally varying reaction product; and sequentially discharging the reaction product of each of combination from the reaction zone as reaction of each combination is completed.

In another aspect, the present invention is directed to a combinatorial chemical synthesis system, comprising a vessel having a charge port adapted to sequentially receive a plurality of discrete combinations of reactants and a reaction chamber in communication with the charge port and adapted to receive and enclose the plurality of reactant combinations disposed linearly within the chamber. A discharge port is placed in communication with the reaction chamber to sequentially discharge reaction products from the reaction chamber.

BRIEF DESCRIPTION OF THE DRAWINGS

Various features, aspects, and advantages of the present invention will become more apparent with reference to the following description, appended claims, and accompanying drawings, wherein

FIG.1 is a schematic representation of an aspect of an embodiment of the present invention;

FIG.2 is a schematic representation of an aspect of an embodiment of the present invention;

FIG.3 is a schematic representation of an aspect of an embodiment of the present invention;

FIG.4 is a table of sequences for carrying out an aspect of an embodiment of the present invention; and.

FIG.5 is a graph showing influence of effects and interactions utilizing an embodiment of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Various embodiments of the present system are capable of fully unattended around the clock operation. Temperature, pressure, reaction time and reactant mix within a vessel reaction chamber can be fully automated to allow complete experimentation within precisely scheduled parameters. Sequential high throughput screening (HTS) methods can be conducted within the tubular reactor. For example, sequentially loaded combinations of reactants can be subjected to a varying parameter of reaction within a reaction zone of the reactor to provide continuously or incrementally varying product. The composition of each sequentially loaded

combination can be controlled along with control of varying parameters of reaction within the reaction zone and sequentially produced products can be detected by a convention detecting means. The detected products can be correlated with the varying parameters of the reaction to provide a nonrandom combinatorial library of product.

These and other features will become apparent from the drawings and following detailed discussion, which by way of example without limitation describes preferred embodiments of the present invention.

FIG.1 is a schematic representation of an exemplary system 10 for sequential combinatorial chemical synthesis. FIG. 1 shows a system 10 including a sequential loader 12, a reaction vessel 14, a controller 16 and a detector 18. Loader 12 is shown having an encasement 20 enclosing an array 22 of vials 24 and a robotic frame 26 that includes an X-Y positioning arm 28 and an extendable vial manipulator 30.

Reaction vessel 14 and controller 16 are shown in more detail in FIG.2. Referring to both FIG.1 and FIG. 2, vessel 14 includes a longitudinal reaction chamber 32 having a charge pipe 34 at a chamber first end 36 and a mechanical exit actuator 38 and a discharge pipe 40 at a chamber second end 42. Charge pipe 34 includes a charge port 44 for receiving sequentially loaded vials 24 from loader 12. Charge pipe 34 provides a conveyance for receiving vials 24 and conveying the vials in a sequential fashion to reaction chamber 32. Charge pipe 34 is provided with at least two valves – a charge actuator 46 and a charge gas lock actuator 48 - that create a charge gas lock zone 50. Similarly, discharge pipe 40 includes a discharge port 52 for discharging vials 24 that have been sequentially transported through discharge pipe 40 from reaction chamber 32. In the embodiment shown, discharge pipe 40 is provided with at least two valves – a discharge gas lock actuator 54 and a discharge actuator 56 that create a discharge gas-lock zone 58.

Further shown in FIG.2 is a gas supply and valving combination that illustrates a preferred feature. A gas pressure generator 60 supplies high pressure gas

via a pipe 62 to charge pipe 34 and via a pipe 64 to charge gas lock zone 50. Also, gas pressure generator 60 supplies high pressure gas via a pipe 66 to discharge gas lock zone 58. Pipe 62 includes a charge lock pressure valve 68 that regulates pressure within charge gas lock zone 50. Pipe 64 includes a vessel valve 70 that regulates pressure within reaction vessel 14. Pipe 66 includes a three way discharge lock pressure valve 72 that regulates pressure within discharge gas lock zone 58 by injecting gas or by releasing pressure via a vent 74 to the atmosphere.

The system can include a controller as shown in FIG.1 and FIG.2. Controller 16 includes a processor 76, which can be a microprocessor, computer or the like. Processor 76 can be controllably connected to any or all of charge actuator 46, charge lock pressure valve 68, charge gas lock actuator 48, vessel valve 70, mechanical exit actuator 38, discharge gas lock actuator 54, vessel valve 70, and discharge actuator 56 via lines 78, 80, 82, 84, 86, 88, and 90 to provide a controlled sequential combinatorial chemical synthesis as hereinafter described.

FIG.1 shows a cut away side view of the reaction vessel 14 showing a stack of vials 24 progressing through longitudinal reaction chamber 32. FIG. 1 also shows an electronic heating jacket 102 encompassing chamber 32. FIG. 3 further shows jacket 102 in combination with a structure for controlling temperature conditions within the chamber 32. The structure includes insulation 104 interposed within jacket 102, a high precision temperature measuring device 106, and a feedback heat controller 108. Examples of the high precision temperature measuring device include a thermocouple, thermistor, or platinum resistance thermometer. Heat controller 108 is attached to the interior of chamber 32 by leads 110. Electronic heating jacket 102 is shown with feedback control via temperature measuring device 106, which can be a probe and heat controller 108. Other combinations can be used to control the temperature in chamber 32 such as a vapor heating jacket with pressure control, so long as the temperature can be controlled to within ±2° C, desirably within ±1° C and preferably within ±0.5° C.

An HTS method can be conducted in the system shown in FIGs.1, 2 and 3. In an exemplary embodiment of the method, an array of catalyst formulations is prepared according to any suitable procedure. For example, one procedure produces a homogeneous chemical reaction utilizing multiphase reactants. In this procedure, a formulation is prepared that represents a first reactant that is at least partially embodied in a liquid. During the subsequent reaction, the liquid of the first reactant can be contacted with a second reactant at least partially embodied in a gas. The liquid forms a film having a thickness sufficient to allow the reaction rate of the chemical reaction to be essentially independent of the mass transport rate of the second reactant into the liquid.

Each thin film formulation is deposited into a vial 24 to provide an array of reaction vials 24. Vial 24 is preferably formed of a rigid material that is chemically inert in the reaction environment. An example of an acceptable vial for many reactions is a glass vial. When dealing with liquids with low vapor pressures or with lengthy reactions, it may be desirable to provide a covering, such as a selectively permeable cap 16 or a septum (not shown) incorporating a feed tube or needle disposed such that a gas is allowed to move freely into and out of vial 24 while depletion of liquid by evaporation is minimized. This arrangement allows an external pressure source to act upon the gas in the reactant environment while evaporation of liquid is limited. In most applications, suitable materials for the cap include polytetrafluoroethylene (PTFE) and expanded PTFE. A suitable cap for use with 2 ml glass vials is "Clear Snap Cap, PTFE/Silicone/PTFE with Starburst, 11mm", part no. 27428, available from Supelco, Inc., Bellefonte, Pennsylvania.

The sequential loader 12 can be coordinated by controller 16 with a valving and actuator sequence described in the table of FIG.4. With reference to FIG.4, at commencement of operations, charge valve actuator 46 and discharge actuator 56 are open and the mechanical exit actuator 38 is deactivated (off); charge gas lock valve 46, charge lock pressure valve 68, vessel pressure valve 70 and discharge gas lock actuator 54 are closed and the three way gas lock valve 72 is in a vent position. The array of vials is positioned within sequential loader 12. Extendable X-Y positioning

arm 28 grasps a vial 24 from the array 22 and positions the vial above charge port 44. Vessel pressure valve 70 is opened. A first vial from the array is charged by positioning arm 28 through open actuator 46 into charge gas lock zone 50 and the actuator is closed. Charge lock pressure valve 68 is opened and the charge lock zone 50 is pressurized to a pressure to match a reaction pressure within reaction chamber 32.

When pressure in charge lock zone 50 matches the reaction chamber pressure, charge lock pressure valve 68 is closed and charge gas lock actuator 48 is actuated to advance vial 24 into reaction chamber 32 and the actuator is closed. At this time, charge valve actuator 46 can be opened and charge gas lock zone 50 vented.

Vial contents are subjected to temperature and pressure reaction conditions within reaction chamber 32. Discharge actuator 56 is closed and three way discharge lock valve 72 is positioned to admit pressured gas from gas pressure generator 60 into discharge gas lock zone 58. Upon completion of reaction of the vial contents, mechanical exit actuator 38 is activated. Mechanical actuator 38 extends an arm immediately above vial 24 to prevent upper vials from dropping when a discharged vial drops from the chamber 32 into discharge gas lock zone 58. Discharge gas lock actuator 54 is then closed. Mechanical actuator 38 withdraws the arm, allowing vials above discharged vial 24 to drop so that the stack is now at the bottom of the tube.

Discharge gas lock zone 58 is depressurized by venting via three way valve 72 and discharge actuator 58 is opened to discharge vial 22 from zone 58 and thence from discharge pipe 40 to detector 18.

The above valve and actuator cycling procedure has been described with reference to processing of a single vial 22. However, a plurality of vials can be processed by repeating the FIG.4 steps 2-8 a plurality of times to fill reaction chamber 32. Once chamber 32 is filled, then steps 2-16 are repeated to discharge a vial and to charge a vial to the reaction chamber.

Referring again to FIG.1, the system also includes detector 18, which comprises a vial ejector 92 to direct a vial 24 from the reaction vessel discharge port 52 to a position within a vial array 94 that is retained on an X-Y positioning stage 96. The sequence of FIG.4 can be coordinated with detector 18. Detector 18 further includes a fiber optic sensor 98 to sense the contents of the vials in combination with an analyzer 100. Analyzer 100 can utilize chromatography, infra red spectroscopy, mass spectroscopy, laser mass spectroscopy, microspectroscopy, NMR or the like to determine the constituency of each vial content.

In operation, X-Y positioning stage 96 of detector 18 positions an opening in array 94 directly beneath discharge port 52 so that when discharged, vial 24 falls cleanly into the array. Controller 16 registers the exact time a vial discharges from reactor vessel 14. X-Y positioning stage 96 moves array 94 beneath fiber optic sensor 98, which senses the contents of vial 24 for analysis by analyzer 100. For example, if the method and system of the invention is used to conduct a combinatorial synthesis to select a carbonylation catalyst and/or to determine optimum carbonylation reaction conditions, the analyzer analyzes the contents of the vial for carbonylated product. In this case, the analyzer can use Raman spectroscopy. The Raman peak is integrated using the analyzer electronics and the resulting data can be stored in the controller. Other analytical methods may be used as noted above.

The sequential combinatorial chemical synthesis herein described can be used with any suitable reactant system. For example, the system and method herein can be used for determining a method for producing diphenyl carbonate (DPC). Diphenyl carbonate (DPC) is useful, *inter alia*, as an intermediate in the preparation of polycarbonates. One method for producing DPC involves the carbonylation of a hydroxyaromatic compound (e.g., phenol) in the presence of a catalyst system. A carbonylation catalyst system typically includes a Group VIII B metal (e.g., palladium), a halide composition, and a combination of inorganic co-catalysts (IOCCs). This one step reaction is typically carried out in a continuous reactor at high temperature and pressure with gas sparging. Insufficient gas/liquid mixing can result in low yields of DPC. Generally, testing of new catalyst systems has been

accomplished at macro-scale and, because the mechanism of this carbonylation reaction is not fully understood, the identity of additional effective IOCCs has eluded practitioners. An embodiment of the present invention allows this homogeneous carbonylation reaction to be carried out in parallel with various potential catalyst systems and, consequently, this embodiment can be used to identify effective IOCCs for the carbonylation of phenol.

The following example is provided in order that those skilled in the art will be better able to understand and practice the present invention. This example is intended to serve as an illustration and not as a limitation of the present invention as defined in the claims herein.

Example

The economics of producing DPC by the above-mentioned carbonylation process is partially dependent on the number of moles of DPC produced per mole of Group VIII B metal utilized. In the following example, the Group VIII B metal utilized is palladium. For convenience, the number of moles of DPC produced per mole of palladium utilized is referred to as the palladium turnover number (Pd TON). Unless otherwise specified, all parts are by weight; all equivalents are relative to palladium; and all reactions are carried out in 2 ml glass vials at 90-100° C in a 10% O_2 in CO atmosphere at an operating pressure of 95-110 atm. Reaction is generally 2-3 hours. Reaction products are verified by gas chromatography.

This example illustrates an identification of an active and selective catalyst for the production of aromatic carbonates. The procedure identifies the best catalyst from a complex chemical space, where the chemical space is defined as an assemblage of all possible experimental conditions defined by a set of variable parameters such as formulation ingredient identity or amount or process parameter such as reaction time, temperature, or pressure. In the Example, an initial iteration examines an experimental formulation consisting of six chemical species shown in TABLE 1 and the process parameters shown in TABLE 2.

TABLE 1

	Formulation Type Parameter Variation	Formulation Amount Parameter Variation
Precious metal catalyst	Held Constant	Held Constant
Metal Catalyst 1 (M1)	Fe, Cu,Ni,Pb,Re (as their acetylacetonates)	5, 20 (as molar ratios to precious metal catalyst)
Metal Catalyst 2 (M2)	V, W, Ce,La,Sn (as their acetylacetonates)	5, 20 (as molar ratios to precious metal catalyst)
Cosolvent (CS)	Dimethylformamide (DMFA), Dimethylacetamide (DMAA), Tetrahydrofuran (THF), Diglyme (DiGly), Diethylacetamide (DEAA)	Varied independently in amount. Values are 500, 4000 (as molar ratios to precious metal catalyst)
Hydroxyaromatic compound	Held constant	Sufficient added to achieve constant sample volume

TABLE 2

Process Parameter	Process Parameter Variation
Pressure	1000 psi, 1500 psi (8% Oxygen in Carbon Monoxide)
Temperature	100 C, 120 C
Reaction Time	1 hour, 2 hours .

The size of the initial chemical space defined by the parameters of TABLE 1 and TABLE 2 is calculated as 8000 possibilities. This is a very large experiment for conventional techniques. In Iteration 1 of the process, a 400-sample subset of the 8000 possibilities is selected to screen formulation factors (M1, M2, and CS) while maintaining full representation of the quantity and process factors. A Latin Square design strategy is applied to generate a 5x5 square of the formulation factors. A Latin Square is an orthogonal design that allows each value of each factor to combine with each value of each other factor exactly once. In the present instance, the Latin Square is represented in abbreviated form in TABLE 3 and fully expanded in TABLE 4.

TABLE 3

		M1				
		Fe	Cu	Ni	Pb	Re
M2	V	DMFA	DMAA	THF	DiGly	DEAA
	W	DMAA	THF	DiGly	DEAA	DMFA
	Ce	THF	DiGly	DEAA	DMFA	DMAA

La	DiGly	DEAA	DMFA	DMAA	THF
Sn	DEAA	DMFA	DMAA	THF	DiGly

TABLE 4

Ml1	Ml2	Cosolvent	TON
Cu	V	DMFA	2158
Cu	W	DMAA	2873
Cu	Ce	THF	1519
Cu	La	DiGly	1416
Cu	Sn	DEAA	1336
Fe	V	DMAA	3695
Fe	W	THF	4012
Fe	Ce	DiGly	2983
Fe	La	DEAA	2882
Fe	Sn	DMFA	3034
Ni	V	THF	347
Ni	W	DiGly	1122
Ni	Ce	DEAA	154
Ni	La	DMFA	44
Ni	Sn	DMAA	252
Pb	V	DiGly	522
Pb	W	DEAA	1127
Pb	Ce	DMFA	102
Pb	La	DMAA	139
Pb	Sn	THF	49

Re	V	DEAA	492
Re	W	DMFA	1184
Re	Ce	DMAA	298
Re	La	THF	89
Re	Sn	DiGly	55

A 16-run 2-level fractional factorial design is generated in the six process variables. A 2-level fractional factorial design is an experiment with >1 adjustable control parameters (factors), each of which takes on 2 values (levels). All possible combinations of the factors and levels are generated. A fraction of the possible combinations is selected to maximize the value of information gained from the experiment. In this Example, six process variables generate 64 possibilities, of which one-fourth is selected according to the fractional factorial design. TABLE 5 shows the selected possibilities.

TABLE 5

M1 amt	M2 amp	CS amt	Pressure	Temp	Time
5.00	20.00	500.00	1000.00	120.00	2.00
20.00	5.00	500.00	1200.00	120.00	2.00
5.00	5.00	500.00	1000.00	100.00	1.00
5.00	5.00	500.00	1200.00	100.00	2.00
5.00	5.00	4000.00	1000.00	120.00	2.00
5.00	20.00	500.00	1200.00	120.00	1.00
5.00	20.00	4000.00	1200.00	100.00	2.00
5.00	5.00	4000.00	1200.00	120.00	1.00
20.00	20.00	500.00	1200.00	100.00	1.00
20.00	20.00	4000.00	1200.00	120.00	2.00
20.00	5.00	4000.00	1000.00	100.00	2.00
20.00	20.00	500.00	1000.00	100.00	2.00
5.00	20.00	4000.00	1000.00	100.00	1.00
20.00	5.00	4000.00	1200.00	100.00	1.00
20.00	20.00	4000.00	1000.00	120.00	1.00
20.00	5.00	500.00	1000.00	120.00	1.00

A composite design is then generated in which each run of the fractional factorial design is performed at each combination of the Latin Square, for a total of 25x16 = 400 samples. The composite design is sorted by pressure, temperature and time as shown in TABLE 6.

TABLE 6

Sample	M1	M2	CS	M1 amt	M2 amt	CS amt	Pressure	Temp	Time
1	Cu	V	DMFA	5	5	500	1000	100	1
2	Cu	V	DMFA	5	20	4000	1000	100	1
3	Cu	W	DMAA	5	5	500	1000	100	1
4	Cu	W	DMAA	5	20	4000	1000	100	1
5	Cu	Ce	THF	5	5	500	1000	100	1
6	Cu	Ce	THF	5	20	4000	1000	100	1
7	Cu	La	DiGly	5	5	500	1000	100	1
8	Cu	La	DiGly	5	20	4000	1000	100	1
9	Cu	Sn	DEAA	5	5	500	1000	100	1
10	Cu	Sn	DEAA	5	20	4000	1000	100	1
11	Fe	V	DMAA	5	5	500	1000	100	1
12	Fe	V	DMAA	5	20	4000	1000	100	1
13	Fe	W	THF	5	5	500	1000	100	1
14	Fe	W	THF	5	20	4000	1000	100	1
15	Fe	Ce	DiGly	5	5	500	1000	100	1

16	Fe	Ce	DiGly	5	20	4000	1000	100	1
17	Fe	La	DEAA	5	5	500	1000	100	1
18	Fe	La	DEAA	5	20	4000	1000	100	1
19	Fe	Sn	DMFA	5	5	500	1000	100	1
20	Fe	Sn	DMFA	5	20	4000	1000	100	1
21	Ni	V	THF	5	5	500	1000	100	1
22	Ni	V	THF	5	20	4000	1000	100	1
23	Ni	W	DiGly	5	5	500	1000	100	1
24	Ni	W	DiGly	5	20	4000	1000	100	1
25	Ni	Ce	DEAA	5	5	500	1000	100	1
26	Ni	Ce	DEAA	5	20	4000	1000	100	1
27	Ni	La	DMFA	5	5	500	1000	100	1
28	Ni	La	DMFA	5	20	4000	1000	100	1
29	Ni	Sn	DMAA	5	5	500	1000	100	1
30	Ni	Sn	DMAA	5	20	4000	1000	100	1
31	Pb	V	DiGly	5	5	500	1000	100	1
32	Pb	V	DiGly	5	20	4000	1000	100	1
33	Pb	W	DEAA	5	5	500	1000	100	1
34	Pb	W	DEAA	5	20	4000	1000	100	1
35	Pb	Ce	DMFA	5	5	500	1000	100	1

36	Pb	Ce	DMFA	5	20	4000	1000	100	1
37	Pb	La	DMAA	5	5	500	1000	100	1
38	Pb	La	DMAA	5	20	4000	1000	100	1
39	Pb	Sn	THF	5	5	500	1000	100	1
40	Pb	Sn	THF	5	20	4000	1000	100	1
41	Re	V	DEAA	5	5	500	1000	100	1
42	Re	V	DEAA	5	20	4000	1000	100	1
43	Re	W	DMFA	5	5	500	1000	100	1
44	Re	W	DMFA	5	20	4000	1000	100	1
45	Re	Ce	DMAA	5	5	500	1000	100	1
46	Re	Ce	DMAA	5	20	4000	1000	100	1
47	Re	La	THF	5	5	500	1000	100	1
48	Re	La	THF	5	20	4000	1000	100	1
49	Re	Sn	DiGly	5	5	500	1000	100	1
50	Re	Sn	DiGly	5	20	4000	1000	100	1
51	Cu	V	DMFA	20	5	4000	1000	100	2
52	Cu	V	DMFA	20	20	500	1000	100	2
53	Cu	W	DMAA	20	5	4000	1000	100	2
54	Cu	W	DMAA	20	20	500	1000	100	2
55	Cu	Ce	THF	20	5	4000	1000	100	2

56	Cu	Ce	THF	20	20	500	1000	100	2
57	Cu	La	DiGly	20	5	4000	1000	100	2
58	Cu	La	DiGly	20	20	500	1000	100	2
59	Cu	Sn	DEAA	20	5	4000	1000	100	2
60	Cu	Sn	DEAA	20	20	500	1000	100	2
61	Fe	V	DMAA	20	5	4000	1000	100	2
62	Fe	V	DMAA	20	20	500	1000	100	2
63	Fe	W	THF	20	5	4000	1000	100	2
64	Fe	W	THF	20	20	500	1000	100	2
65	Fe	Ce	DiGly	20	5	4000	1000	100	2
66	Fe	Ce	DiGly	20	20	500	1000	100	2
67	Fe	La	DEAA	20	5	4000	1000	100	2
68	Fe	La	DEAA	20	20	500	1000	100	2
69	Fe	Sn	DMFA	20	5	4000	1000	100	2
70	Fe	Sn	DMFA	20	20	500	1000	100	2
71	Ni	V	THF	20	5	4000	1000	100	2
72	Ni	V	THF	20	20	500	1000	100	2
73	Ni	W	DiGly	20	5	4000	1000	100	2
74	Ni	W	DiGly	20	20	500	1000	100	2
75	Ni	Ce	DEAA	20	5	4000	1000	100	2

76	Ni	Ce	DEAA	20	20	500	1000	100	2
77	Ni	La	DMFA	20	5	4000	1000	100	2
78	Ni	La	DMFA	20	20	500	1000	100	2
79	Ni	Sn	DMAA	20	5	4000	1000	100	2
80	Ni	Sn	DMAA	20	20	500	1000	100	2
81	Pb	V	DiGly	20	5	4000	1000	100	2
82	Pb	V	DiGly	20	20	500	1000	100	2
83	Pb	W	DEAA	20	5	4000	1000	100	2
84	Pb	W	DEAA	20	20	500	1000	100	2
85	Pb	Ce	DMFA	20	5	4000	1000	100	2
86	Pb	Ce	DMFA	20	20	500	1000	100	2
87	Pb	La	DMAA	20	5	4000	1000	100	2
88	Pb	La	DMAA	20	20	500	1000	100	2
89	Pb	Sn	THF	20	5	4000	1000	100	2
90	Pb	Sn	THF	20	20	500	1000	100	2
91	Re	V	DEAA	20	5	4000	1000	100	2
92	Re	V	DEAA	20	20	500	1000	100	2
93	Re	W	DMFA	20	5	4000	1000	100	2
94	Re	W	DMFA	20	20	500	1000	100	2
95	Re	Ce	DMAA	20	5	4000	1000	100	2

96	Re	Ce	DMAA	20	20	500	1000	100	2
97	Re	La	THF	20	5	4000	1000	100	2
98	Re	La	THF	20	20	500	1000	100	2
99	Re	Sn	DiGly	20	5	4000	1000	100	2
100	Re	Sn	DiGly	20	20	500	1000	100	2
101	Cu	V	DMFA	20	20	4000	1000	120	1
102	Cu	V	DMFA	20	5	500	1000	120	1
103	Cu	W	DMAA	20	20	4000	1000	120	1
104	Cu	W	DMAA	20	5	500	1000	120	1
105	Cu	Ce	THF	20	20	4000	1000	120	1
106	Cu	Ce	THF	20	5	500	1000	120	1
107	Cu	La	DiGly	20	20	4000	1000	120	1
108	Cu	La	DiGly	20	5	500	1000	120	1
109	Cu	Sn	DEAA	20	20	4000	1000	120	1
110	Cu	Sn	DEAA	20	5	500	1000	120	1
111	Fe	V	DMAA	20	20	4000	1000	120	1
112	Fe	V	DMAA	20	5	500	1000	120	1
113	Fe	W	THF	20	20	4000	1000	120	1
114	Fe	W	THF	20	5	500	1000	120	1
115	Fe	Ce	DiGly	20	20	4000	1000	120	1

116	Fe	Ce	DiGly	20	5	500	1000	120	1
117	Fe	La	DEAA	20	20	4000	1000	120	1
118	Fe	La	DEAA	20	5	500	1000	120	1
119	Fe	Sn	DMFA	20	20	4000	1000	120	1
120	Fe	Sn	DMFA	20	5	500	1000	120	1
121	Ni	V	THF	20	20	4000	1000	120	1
122	Ni	V	THF	20	5	500	1000	120	1
123	Ni	W	DiGly	20	20	4000	1000	120	1
124	Ni	W	DiGly	20	5	500	1000	120	1
125	Ni	Ce	DEAA	20	20	4000	1000	120	1
126	Ni	Ce	DEAA	20	5	500	1000	120	1
127	Ni	La	DMFA	20	20	4000	1000	120	1
128	Ni	La	DMFA	20	5	500	1000	120	1
129	Ni	Sn	DMAA	20	20	4000	1000	120	1
130	Ni	Sn	DMAA	20	5	500	1000	120	1
131	Pb	V	DiGly	20	20	4000	1000	120	1
132	Pb	V	DiGly	20	5	500	1000	120	1
133	Pb	W	DEAA	20	20	4000	1000	120	1
134	Pb	W	DEAA	20	5	500	1000	120	1
135	Pb	Ce	DMFA	20	20	4000	1000	120	1

136	Pb	Ce	DMFA	20	5	500	1000	120	1
137	Pb	La	DMAA	20	20	4000	1000	120	1
138	Pb	La	DMAA	20	5	500	1000	120	1
139	Pb	Sn	THF	20	20	4000	1000	120	1
140	Pb	Sn	THF	20	5	500	1000	120	1
141	Re	V	DEAA	20	20	4000	1000	120	1
142	Re	V	DEAA	20	5	500	1000	120	1
143	Re	W	DMFA	20	20	4000	1000	120	1
144	Re	W	DMFA	20	5	500	1000	120	1
145	Re	Ce	DMAA	20	20	4000	1000	120	1
146	Re	Ce	DMAA	20	5	500	1000	120	1
147	Re	La	THF	20	20	4000	1000	120	1
148	Re	La	THF	20	5	500	1000	120	1
149	Re	Sn	DiGly	20	20	4000	1000	120	1
150	Re	Sn	DiGly	20	5	500	1000	120	1
151	Cu	V	DMFA	5	20	500	1000	120	2
152	Cu	V	DMFA	5	5	4000	1000	120	2
153	Cu	W	DMAA	5	20	500	1000	120	2
154	Cu	W	DMAA	5	5	4000	1000	120	2
155	Cu	Ce	THF	5	20	500	1000	120	2

156	Cu	Ce	THF	5	5	4000	1000	120	2
157	Cu	La	DiGly	5	20	500	1000	120	2
158	Cu	La	DiGly	5	5	4000	1000	120	2
159	Cu	Sn	DEAA	5	20	500	1000	120	2
160	Cu	Sn	DEAA	5	5	4000	1000	120	2
161	Fe	V	DMAA	5	20	500	1000	120	2
162	Fe	V	DMAA	5	5	4000	1000	120	2
163	Fe	W	THF	5	20	500	1000	120	2
164	Fe	W	THF	5	5	4000	1000	120	2
165	Fe	Ce	DiGly	5	20	500	1000	120	2
166	Fe	Ce	DiGly	5	5	4000	1000	120	2
167	Fe	La	DEAA	5	20	500	1000	120	2
168	Fe	La	DEAA	5	5	4000	1000	120	2
169	Fe	Sn	DMFA	5	20	500	1000	120	2
170	Fe	Sn	DMFA	5	5	4000	1000	120	2
171	Ni	V	THF	5	20	500	1000	120	2
172	Ni	V	THF	5	5	4000	1000	120	2
173	Ni	W	DiGly	5	20	500	1000	120	2
174	Ni	W	DiGly	5	5	4000	1000	120	2
175	Ni	Ce	DEAA	5	20	500	1000	120	2

176	Ni	Ce	DEAA	5	5	4000	1000	120	2
177	Ni	La	DMFA	5	20	500	1000	120	2
178	Ni	La	DMFA	5	5	4000	1000	120	2
179	Ni	Sn	DMAA	5	20	500	1000	120	2
180	Ni	Sn	DMAA	5	5	4000	1000	120	2
181	Pb	V	DiGly	5	20	500	1000	120	2
182	Pb	V	DiGly	5	5	4000	1000	120	2
183	Pb	W	DEAA	5	20	500	1000	120	2
184	Pb	W	DEAA	5	5	4000	1000	120	2
185	Pb	Ce	DMFA	5	20	500	1000	120	2
186	Pb	Ce	DMFA	5	5	4000	1000	120	2
187	Pb	La	DMAA	5	20	500	1000	120	2
188	Pb	La	DMAA	5	5	4000	1000	120	2
189	Pb	Sn	THF	5	20	500	1000	120	2
190	Pb	Sn	THF	5	5	4000	1000	120	2
191	Re	V	DEAA	5	20	500	1000	120	2
192	Re	V	DEAA	5	5	4000	1000	120	2
193	Re	W	DMFA	5	20	500	1000	120	2
194	Re	W	DMFA	5	5	4000	1000	120	2
195	Re	Ce	DMAA	5	20	500	1000	120	2

196	Re	Ce	DMAA	5	5	4000	1000	120	2
197	Re	La	THF	5	20	500	1000	120	2
198	Re	La	THF	5	5	4000	1000	120	2
199	Re	Sn	DiGly	5	20	500	1000	120	2
200	Re	Sn	DiGly	5	5	4000	1000	120	2
201	Cu	V	DMFA	20	20	500	1200	100	1
202	Cu	V	DMFA	20	5	4000	1200	100	1
203	Cu	W	DMAA	20	20	500	1200	100	1
204	Cu	W	DMAA	20	5	4000	1200	100	1
205	Cu	Ce	THF	20	20	500	1200	100	1
206	Cu	Ce	THF	20	5	4000	1200	100	1
207	Cu	La	DiGly	20	20	500	1200	100	1
208	Cu	La	DiGly	20	5	4000	1200	100	1
209	Cu	Sn	DEAA	20	20	500	1200	100	1
210	Cu	Sn	DEAA	20	5	4000	1200	100	1
211	Fe	V	DMAA	20	20	500	1200	100	1
212	Fe	V	DMAA	20	5	4000	1200	100	1
213	Fe	W	THF	20	20	500	1200	100	1
214	Fe	W	THF	20	5	4000	1200	100	1
215	Fe	Ce	DiGly	20	20	500	1200	100	1

216	Fe	Ce	DiGly	20	5	4000	1200	100	1
217	Fe	La	DEAA	20	20	500	1200	100	1
218	Fe	La	DEAA	20	5	4000	1200	100	1
219	Fe	Sn	DMFA	20	20	500	1200	100	1
220	Fe	Sn	DMFA	20	5	4000	1200	100	1
221	Ni	V	THF	20	20	500	1200	100	1
222	Ni	V	THF	20	5	4000	1200	100	1
223	Ni	W	DiGly	20	20	500	1200	100	1
224	Ni	W	DiGly	20	5	4000	1200	100	1
225	Ni	Ce	DEAA	20	20	500	1200	100	1
226	Ni	Ce	DEAA	20	5	4000	1200	100	1
227	Ni	La	DMFA	20	20	500	1200	100	1
228	Ni	La	DMFA	20	5	4000	1200	100	1
229	Ni	Sn	DMAA	20	20	500	1200	100	1
230	Ni	Sn	DMAA	20	5	4000	1200	100	1
231	Pb	V	DiGly	20	20	500	1200	100	1
232	Pb	V	DiGly	20	5	4000	1200	100	1
233	Pb	W	DEAA	20	20	500	1200	100	1
234	Pb	W	DEAA	20	5	4000	1200	100	1
235	Pb	Ce	DMFA	20	20	500	1200	100	1

236	Pb	Ce	DMFA	20	5	4000	1200	100	1
237	Pb	La	DMAA	20	20	500	1200	100	1
238	Pb	La	DMAA	20	5	4000	1200	100	1
239	Pb	Sn	THF	20	20	500	1200	100	1
240	Pb	Sn	THF	20	5	4000	1200	100	1
241	Re	V	DEAA	20	20	500	1200	100	1
242	Re	V	DEAA	20	5	4000	1200	100	1
243	Re	W	DMFA	20	20	500	1200	100	1
244	Re	W	DMFA	20	5	4000	1200	100	1
245	Re	Ce	DMAA	20	20	500	1200	100	1
246	Re	Ce	DMAA	20	5	4000	1200	100	1
247	Re	La	THF	20	20	500	1200	100	1
248	Re	La	THF	20	5	4000	1200	100	1
249	Re	Sn	DiGly	20	20	500	1200	100	1
250	Re	Sn	DiGly	20	5	4000	1200	100	1
251	Cu	V	DMFA	5	5	500	1200	100	2
252	Cu	V	DMFA	5	20	4000	1200	100	2
253	Cu	W	DMAA	5	5	500	1200	100	2
254	Cu	W	DMAA	5	20	4000	1200	100	2
255	Cu	Ce	THF	5	5	500	1200	100	2

256	Cu	Ce	THF	5	20	4000	1200	100	2
257	Cu	La	DiGly	5	5	500	1200	100	2
258	Cu	La	DiGly	5	20	4000	1200	100	2
259	Cu	Sn	DEAA	5	5	500	1200	100	2
260	Cu	Sn	DEAA	5	20	4000	1200	100	2
261	Fe	V	DMAA	5	5	500	1200	100	2
262	Fe	V	DMAA	5	20	4000	1200	100	2
263	Fe	W	THF	5	5	500	1200	100	2
264	Fe	W	THF	5	20	4000	1200	100	2
265	Fe	Ce	DiGly	5	5	500	1200	100	2
266	Fe	Ce	DiGly	5	20	4000	1200	100	2
267	Fe	La	DEAA	5	5	500	1200	100	2
268	Fe	La	DEAA	5	20	4000	1200	100	2
269	Fe	Sn	DMFA	5	5	500	1200	100	2
270	Fe	Sn	DMFA	5	20	4000	1200	100	2
271	Ni	V	THF	5	5	500	1200	100	2
272	Ni	V	THF	5	20	4000	1200	100	2
273	Ni	W	DiGly	5	5	500	1200	100	2
274	Ni	W	DiGly	5	20	4000	1200	100	2
275	Ni	Ce	DEAA	5	5	500	1200	100	2

276	Ni	Ce	DEAA	5	20	4000	1200	100	2
277	Ni	La	DMFA	5	5	500	1200	100	2
278	Ni	La	DMFA	5	20	4000	1200	100	2
279	Ni	Sn	DMAA	5	5	500	1200	100	2
280	Ni	Sn	DMAA	5	20	4000	1200	100	2
281	Pb	V	DiGly	5	5	500	1200	100	2
282	Pb	V	DiGly	5	20	4000	1200	100	2
283	Pb	W	DEAA	5	5	500	1200	100	2
284	Pb	W	DEAA	5	20	4000	1200	100	2
285	Pb	Ce	DMFA	5	5	500	1200	100	2
286	Pb	Ce	DMFA	5	20	4000	1200	100	2
287	Pb	La	DMAA	5	5	500	1200	100	2
288	Pb	La	DMAA	5	20	4000	1200	100	2
289	Pb	Sn	THF	5	5	500	1200	100	2
290	Pb	Sn	THF	5	20	4000	1200	100	2
291	Re	V	DEAA	5	5	500	1200	100	2
292	Re	V	DEAA	5	20	4000	1200	100	2
293	Re	W	DMFA	5	5	500	1200	100	2
294	Re	W	DMFA	5	20	4000	1200	100	2
295	Re	Ce	DMAA	5	5	500	1200	100	2

296	Re	Ce	DMAA	5	20	4000	1200	100	2
297	Re	La	THF	5	5	500	1200	100	2
298	Re	La	THF	5	20	4000	1200	100	2
299	Re	Sn	DiGly	5	5	500	1200	100	2
300	Re	Sn	DiGly	5	20	4000	1200	100	2
301	Cu	V	DMFA	5	20	500	1200	120	1
302	Cu	V	DMFA	5	5	4000	1200	120	1
303	Cu	W	DMAA	5	20	500	1200	120	1
304	Cu	W	DMAA	5	5	4000	1200	120	1
305	Cu	Ce	THF	5	20	500	1200	120	1
306	Cu	Ce	THF	5	5	4000	1200	120	1
307	Cu	La	DiGly	5	20	500	1200	120	1
308	Cu	La	DiGly	5	5	4000	1200	120	1
309	Cu	Sn	DEAA	5	20	500	1200	120	1
310	Cu	Sn	DEAA	5	5	4000	1200	120	1
311	Fe	V	DMAA	5	20	500	1200	120	1
312	Fe	V	DMAA	5	5	4000	1200	120	1
313	Fe	W	THF	5	20	500	1200	120	1
314	Fe	W	THF	5	5	4000	1200	120	1
315	Fe	Ce	DiGly	5	20	500	1200	120	1

316	Fe	Ce	DiGly	5	5	4000	1200	120	1
317	Fe	La	DEAA	5	20	500	1200	120	1
318	Fe	La	DEAA	5	5	4000	1200	120	1
319	Fe	Sn	DMFA	5	20	500	1200	120	1
320	Fe	Sn	DMFA	5	5	4000	1200	120	1
321	Ni	V	THF	5	20	500	1200	120	1
322	Ni	V	THF	5	5	4000	1200	120	1
323	Ni	W	DiGly	5	20	500	1200	120	1
324	Ni	W	DiGly	5	5	4000	1200	120	1
325	Ni	Ce	DEAA	5	20	500	1200	120	1
326	Ni	Ce	DEAA	5	5	4000	1200	120	1
327	Ni	La	DMFA	5	20	500	1200	120	1
328	Ni	La	DMFA	5	5	4000	1200	120	1
329	Ni	Sn	DMAA	5	20	500	1200	120	1
330	Ni	Sn	DMAA	5	5	4000	1200	120	1
331	Pb	V	DiGly	5	20	500	1200	120	1
332	Pb	V	DiGly	5	5	4000	1200	120	1
333	Pb	W	DEAA	5	20	500	1200	120	1
334	Pb	W	DEAA	5	5	4000	1200	120	1
335	Pb	Ce	DMFA	5	20	500	1200	120	1

336	Pb	Ce	DMFA	5	5	4000	1200	120	1
337	Pb	La	DMAA	5	20	500	1200	120	1
338	Pb	La	DMAA	5	5	4000	1200	120	1
339	Pb	Sn	THF	5	20	500	1200	120	1
340	Pb	Sn	THF	5	5	4000	1200	120	1
341	Re	V	DEAA	5	20	500	1200	120	1
342	Re	V	DEAA	5	5	4000	1200	120	1
343	Re	W	DMFA	5	20	500	1200	120	1
344	Re	W	DMFA	5	5	4000	1200	120	1
345	Re	Ce	DMAA	5	20	500	1200	120	1
346	Re	Ce	DMAA	5	5	4000	1200	120	1
347	Re	La	THF	5	20	500	1200	120	1
348	Re	La	THF	5	5	4000	1200	120	1
349	Re	Sn	DiGly	5	20	500	1200	120	1
350	Re	Sn	DiGly	5	5	4000	1200	120	1
351	Cu	V	DMFA	20	5	500	1200	120	2
352	Cu	V	DMFA	20	20	4000	1200	120	2
353	Cu	W	DMAA	20	5	500	1200	120	2
354	Cu	W	DMAA	20	20	4000	1200	120	2
355	Cu	Ce	THF	20	5	500	1200	120	2

356	Cu	Ce	THF	20	20	4000	1200	120	2
357	Cu	La	DiGly	20	5	500	1200	120	2
358	Cu	La	DiGly	20	20	4000	1200	120	2
359	Cu	Sn	DEAA	20	5	500	1200	120	2
360	Cu	Sn	DEAA	20	20	4000	1200	120	2
361	Fe	V	DMAA	20	5	500	1200	120	2
362	Fe	V	DMAA	20	20	4000	1200	120	2
363	Fe	W	THF	20	5	500	1200	120	2
364	Fe	W	THF	20	20	4000	1200	120	2
365	Fe	Ce	DiGly	20	5	500	1200	120	2
366	Fe	Ce	DiGly	20	20	4000	1200	120	2
367	Fe	La	DEAA	20	5	500	1200	120	2
368	Fe	La	DEAA	20	20	4000	1200	120	2
369	Fe	Sn	DMFA	20	5	500	1200	120	2
370	Fe	Sn	DMFA	20	20	4000	1200	120	2
371	Ni	V	THF	20	5	500	1200	120	2
372	Ni	V	THF	20	20	4000	1200	120	2
373	Ni	W	DiGly	20	5	500	1200	120	2
374	Ni	W	DiGly	20	20	4000	1200	120	2
375	Ni	Ce	DEAA	20	5	500	1200	120	2

376	Ni	Ce	DEAA	20	20	4000	1200	120	2
377	Ni	La	DMFA	20	5	500	1200	120	2
378	Ni	La	DMFA	20	20	4000	1200	120	2
379	Ni	Sn	DMAA	20	5	500	1200	120	2
380	Ni	Sn	DMAA	20	20	4000	1200	120	2
381	Pb	V	DiGly	20	5	500	1200	120	2
382	Pb	V	DiGly	20	20	4000	1200	120	2
383	Pb	W	DEAA	20	5	500	1200	120	2
384	Pb	W	DEAA	20	20	4000	1200	120	2
385	Pb	Ce	DMFA	20	5	500	1200	120	2
386	Pb	Ce	DMFA	20	20	4000	1200	120	2
387	Pb	La	DMAA	20	5	500	1200	120	2
388	Pb	La	DMAA	20	20	4000	1200	120	2
389	Pb	Sn	THF	20	5	500	1200	120	2
390	Pb	Sn	THF	20	20	4000	1200	120	2
391	Re	V	DEAA	20	5	500	1200	120	2
392	Re	V	DEAA	20	20	4000	1200	120	2
393	Re	W	DMFA	20	5	500	1200	120	2
394	Re	W	DMFA	20	20	4000	1200	120	2
395	Re	Ce	DMAA	20	5	500	1200	120	2

396	Re	Ce	DMAA	20	20	4000	1200	120	2
397	Re	La	THF	20	5	500	1200	120	2
398	Re	La	THF	20	20	4000	1200	120	2
399	Re	Sn	DiGly	20	5	500	1200	120	2
400	Re	Sn	DiGly	20	20	4000	1200	120	2

In this evaluation, each of the metal acetylacetonates, the DMAA, and the DMFA is made up as a stock solution in phenol. An appropriate quantity of each stock solution is then combined using a Hamilton MicroLab 4000 laboratory robot into a single vial for mixing. For example, the stock solutions to produce vials 1, 65, 129,193, 257, 321, 385, and 449, are 0.01 molar Pd(acetylacetonate), 0.01 molar each of Fe(acetylacetonate) and V(acetylacetonate) and 5 molar DMFA. Ten ml of each stock solution is produced by manual weighing and mixing. Aliquots of the stock solutions are measured as follows in TABLE 7. The mixture is stirred using a miniature magnetic stirrer, and then 25 microliters are measured out to each of eight 2-ml vials using the Hamilton robot. This small quantity forms a thin film on the vial bottom.

TABLE 7

0.01 molar Pd(acetylacetonate)	25 microliters
0.01 molar Fe(acetylacetonate)	125 microliters
0.01 molar V(acetylacetonate)	125 microliters
5 molar DMFA	25 microliters
Pure Phenol	700 microliters

After each mixture is made, mixed, and distributed to 2-ml vials, the vials are capped using “star” caps (which allow gas exchange with the environment) and placed in the loader of FIG.1. The tubular reactor system is heated and pressurized to the conditions shown as Block 1 in TABLE 8 and the automatic loading and processing procedure discussed above is begun. Loading and unloading times are controlled so that each vial is in the heated reaction zone for the time shown in Block 1: 1 hour. The reaction zone can accommodate a stack of 20 vials. A new vial is added every three minutes until the stack is full, then one vial is removed and another added every three minutes thereafter. As vials progress down the stack, their exposure time is 20 x 3 minutes = 60 minutes = 1 hour.

TABLE 8

Block	Pressure (psi)	Temperature (°C)	Time (hours)
1	1000	100	1
2	1000	100	2
3	1000	120	1
4	1000	120	2
5	1200	100	1
6	1200	100	2
7	1200	120	1
8	1200	120	2

As each vial exits the reactor, it falls into a new array and is analyzed by gas-liquid chromatography.

Performance is expressed numerically as a catalyst turnover number or TON. TON is defined as the number of moles of aromatic carbonate produced per mole of Palladium catalyst charged.

When all rows with the same pressure, temperature and reaction time have been processed, the pressure and temperature are adjusted to new conditions. The timing is adjusted and a next row is processed. This iteration is repeated until all conditions have been run. The performance of each vial is given in the column "TON" of TABLE 4. The TON's of TABLE 4 are averaged by each formulation component to give the results shown in TABLE 9. TAB:LE 9 shows that average TON is significantly larger for M1 = Fe or Cu; M2= V or W; and cosolvent = DMFA or DMAA. These are selected for a second iteration.

TABLE 9

M1	M1ave	M2	M2ave	Cosolvent	CS ave
Cu	1860.3	V	1442.8	DMFA	1304.4
Fe	3321.5	W	2063.5	DMAA	1451.5
Ni	383.8	Ce	1011.2	THF	1203.1
Pb	387.7	La	914.1	DiGly	1219.5
Re	423.7	Sn	945.3	DEAA	1198.4

In the second iteration of the process, experimental formulations consist of six chemical species shown in TABLE 10. Process parameters are shown in TABLE 11.

TABLE 10

	Formulation Type Parameter Variation	Formulation Amount Parameter Variation
Precious metal catalyst	Held Constant	Held Constant
Metal Catalyst 1 (M1)	Fe or Cu (as their acetylacetonates)	5,20 (as molar ratios to precious metal catalyst)
Metal Catalyst 2 (M2)	V or W (as their acetylacetonates)	5,20 (as molar ratios to precious metal catalyst)
Cosolvent (CS)	Dimethylformamide	Varied independently in

	(DMFA) or Dimethylacetamide (DMAA)	amount. Possible values were 500, 4000 (as molar ratios to precious metal catalyst)
Hydroxyaromatic compound	Held constant	Sufficient added to achieve constant sample volume

TABLE 11

Process Parameter	Process Parameter Variation
Pressure	1000 psi, 1500 psi (8% Oxygen in Carbon Monoxide)
Temperature	100 C, 120 C
Reaction Time	1 hour, 2 hours

Size of an initial chemical space defined by the parameters of TABLE 10 and TABLE 11 is calculated as 512 possibilities. The 512 possibilities are organized into an experiment of the type known as a "full factorial design" with pressure, temperature, and reaction time parameters "blocked." A full factorial design is an experiment with >1 adjustable control parameters (factors) each of which can take on >1 value (levels). In a full factorial design experiment, an observation is taken at each of all possible combinations of levels that can be formed from the different factors. A full factorial design is capable of estimating all possible effects of the factors, including main effects and all interactions. The design is necessary where the intention of an experiment is to determine if there are unusual interactions, particularly between process and formulation variables. Where factors are "blocked," factors that are relatively difficult to quickly vary are grouped together. A full factorial design for the chemical space of this Example is shown in TABLE 12.

Block	M1	M1 amt	M2	M2 amt	CS	CS amt	Pressure	Temperature	Time	TON
1	Fe	5	V	5	DMFA	500	1000	100	1	1693.92
1	Cu	5	V	5	DMFA	500	1000	100	1	4091.21
1	Fe	20	V	5	DMFA	500	1000	100	1	1845.361
1	Cu	20	V	5	DMFA	500	1000	100	1	4038.68
1	Fe	5	W	5	DMFA	500	1000	100	1	1754.727
1	Cu	5	W	5	DMFA	500	1000	100	1	3956.726
1	Fe	20	W	5	DMFA	500	1000	100	1	1903.599
1	Cu	20	W	5	DMFA	500	1000	100	1	3676.381
1	Fe	5	V	20	DMFA	500	1000	100	1	2237.44
1	Cu	5	V	20	DMFA	500	1000	100	1	4171.727
1	Fe	20	V	20	DMFA	500	1000	100	1	2665.677
1	Cu	20	V	20	DMFA	500	1000	100	1	4063.274
1	Fe	5	W	20	DMFA	500	1000	100	1	1741.315
1	Cu	5	W	20	DMFA	500	1000	100	1	4263.502
1	Fe	20	W	20	DMFA	500	1000	100	1	2264.471
1	Cu	20	W	20	DMFA	500	1000	100	1	3990.751
1	Fe	5	V	5	DMAA	500	1000	100	1	1862.09
1	Cu	5	V	5	DMAA	500	1000	100	1	4000.029
1	Fe	20	V	5	DMAA	500	1000	100	1	1905.142
1	Cu	20	V	5	DMAA	500	1000	100	1	4195.94
1	Fe	5	W	5	DMAA	500	1000	100	1	2160.141
1	Cu	5	W	5	DMAA	500	1000	100	1	4556.547
1	Fe	20	W	5	DMAA	500	1000	100	1	2219.635
1	Cu	20	W	5	DMAA	500	1000	100	1	3939.92
1	Fe	5	V	20	DMAA	500	1000	100	1	2084.011
1	Cu	5	V	20	DMAA	500	1000	100	1	4214.699
1	Fe	20	V	20	DMAA	500	1000	100	1	2043.003
1	Cu	20	V	20	DMAA	500	1000	100	1	3939.684
1	Fe	5	W	20	DMAA	500	1000	100	1	1659.084
1	Cu	5	W	20	DMAA	500	1000	100	1	3834.039
1	Fe	20	W	20	DMAA	500	1000	100	1	1840.703
1	Cu	20	W	20	DMAA	500	1000	100	1	4183.744
1	Fe	5	V	5	DMFA	4000	1000	100	1	4451.489
1	Cu	5	V	5	DMFA	4000	1000	100	1	2199.05
1	Fe	20	V	5	DMFA	4000	1000	100	1	4345.231
1	Cu	20	V	5	DMFA	4000	1000	100	1	2177.339
1	Fe	5	W	5	DMFA	4000	1000	100	1	4439.784
1	Cu	5	W	5	DMFA	4000	1000	100	1	1915.281
1	Fe	20	W	5	DMFA	4000	1000	100	1	3416.777
1	Cu	20	W	5	DMFA	4000	1000	100	1	1906.395
1	Fe	5	V	20	DMFA	4000	1000	100	1	3955.658
1	Cu	5	V	20	DMFA	4000	1000	100	1	2068.799
1	Fe	20	V	20	DMFA	4000	1000	100	1	3757.099
1	Cu	20	V	20	DMFA	4000	1000	100	1	2195.421
1	Fe	5	W	20	DMFA	4000	1000	100	1	4265.04
1	Cu	5	W	20	DMFA	4000	1000	100	1	2622.194
1	Fe	20	W	20	DMFA	4000	1000	100	1	4080.135
1	Cu	20	W	20	DMFA	4000	1000	100	1	2165.103
1	Fe	5	V	5	DMAA	4000	1000	100	1	3917.162
1	Cu	5	V	5	DMAA	4000	1000	100	1	2401.285
1	Fe	20	V	5	DMAA	4000	1000	100	1	3756.023
1	Cu	20	V	5	DMAA	4000	1000	100	1	1860.372
1	Fe	5	W	5	DMAA	4000	1000	100	1	3812.629
1	Cu	5	W	5	DMAA	4000	1000	100	1	1539.843
1	Fe	20	W	5	DMAA	4000	1000	100	1	4062.504
1	Cu	20	W	5	DMAA	4000	1000	100	1	2322.649
1	Fe	5	V	20	DMAA	4000	1000	100	1	4085.449
1	Cu	5	V	20	DMAA	4000	1000	100	1	1662.921
1	Fe	20	V	20	DMAA	4000	1000	100	1	4030.069
1	Cu	20	V	20	DMAA	4000	1000	100	1	2271.779
1	Fe	5	W	20	DMAA	4000	1000	100	1	4267.062
1	Cu	5	W	20	DMAA	4000	1000	100	1	2020.112
1	Fe	20	W	20	DMAA	4000	1000	100	1	4066.339
1	Cu	20	W	20	DMAA	4000	1000	100	1	1900.791
2	Fe	5	V	5	DMFA	500	1000	100	2	3700.711
2	Cu	5	V	5	DMFA	500	1000	100	2	5105.03
2	Fe	20	V	5	DMFA	500	1000	100	2	3043.119
2	Cu	20	V	5	DMFA	500	1000	100	2	4908.279
2	Fe	5	W	5	DMFA	500	1000	100	2	2899.673

2	Cu	5	W	5	DMFA	500	1000	100	2	4806.417
2	Fe	20	W	5	DMFA	500	1000	100	2	3321.028
2	Cu	20	W	5	DMFA	500	1000	100	2	5529.844
2	Fe	5	V	20	DMFA	500	1000	100	2	3145.139
2	Cu	5	V	20	DMFA	500	1000	100	2	5495.893
2	Fe	20	V	20	DMFA	500	1000	100	2	2599.752
2	Cu	20	V	20	DMFA	500	1000	100	2	4521.231
2	Fe	5	W	20	DMFA	500	1000	100	2	3139.919
2	Cu	5	W	20	DMFA	500	1000	100	2	5106.096
2	Fe	20	W	20	DMFA	500	1000	100	2	3252.493
2	Cu	20	W	20	DMFA	500	1000	100	2	5025.739
2	Fe	5	V	5	DMAA	500	1000	100	2	2801.16
2	Cu	5	V	5	DMAA	500	1000	100	2	5625.641
2	Fe	20	V	5	DMAA	500	1000	100	2	2995.132
2	Cu	20	V	5	DMAA	500	1000	100	2	4854.658
2	Fe	5	W	5	DMAA	500	1000	100	2	2743.656
2	Cu	5	W	5	DMAA	500	1000	100	2	4617.833
2	Fe	20	W	5	DMAA	500	1000	100	2	3023.491
2	Cu	20	W	5	DMAA	500	1000	100	2	5087.621
2	Fe	5	V	20	DMAA	500	1000	100	2	3259.962
2	Cu	5	V	20	DMAA	500	1000	100	2	5375.063
2	Fe	20	V	20	DMAA	500	1000	100	2	2816.106
2	Cu	20	V	20	DMAA	500	1000	100	2	4596.62
2	Fe	5	W	20	DMAA	500	1000	100	2	3301.399
2	Cu	5	W	20	DMAA	500	1000	100	2	5095.495
2	Fe	20	W	20	DMAA	500	1000	100	2	3062.839
2	Cu	20	W	20	DMAA	500	1000	100	2	4980.406
2	Fe	5	V	5	DMFA	4000	1000	100	2	5301.676
2	Cu	5	V	5	DMFA	4000	1000	100	2	2992.894
2	Fe	20	V	5	DMFA	4000	1000	100	2	5226.527
2	Cu	20	V	5	DMFA	4000	1000	100	2	3229.047
2	Fe	5	W	5	DMFA	4000	1000	100	2	4741.478
2	Cu	5	W	5	DMFA	4000	1000	100	2	3150.125
2	Fe	20	W	5	DMFA	4000	1000	100	2	4602.754
2	Cu	20	W	5	DMFA	4000	1000	100	2	2719.743
2	Fe	5	V	20	DMFA	4000	1000	100	2	5004.734
2	Cu	5	V	20	DMFA	4000	1000	100	2	3115.677
2	Fe	20	V	20	DMFA	4000	1000	100	2	4969.642
2	Cu	20	V	20	DMFA	4000	1000	100	2	2806.752
2	Fe	5	W	20	DMFA	4000	1000	100	2	4879.942
2	Cu	5	W	20	DMFA	4000	1000	100	2	2891.03
2	Fe	20	W	20	DMFA	4000	1000	100	2	4912.866
2	Cu	20	W	20	DMFA	4000	1000	100	2	3036.185
2	Fe	5	V	5	DMAA	4000	1000	100	2	4437.605
2	Cu	5	V	5	DMAA	4000	1000	100	2	2880.5
2	Fe	20	V	5	DMAA	4000	1000	100	2	5043.313
2	Cu	20	V	5	DMAA	4000	1000	100	2	2875.502
2	Fe	5	W	5	DMAA	4000	1000	100	2	4705.449
2	Cu	5	W	5	DMAA	4000	1000	100	2	3012.273
2	Fe	20	W	5	DMAA	4000	1000	100	2	5032.286
2	Cu	20	W	5	DMAA	4000	1000	100	2	2658.891
2	Fe	5	V	20	DMAA	4000	1000	100	2	4690.863
2	Cu	5	V	20	DMAA	4000	1000	100	2	2695.653
2	Fe	20	V	20	DMAA	4000	1000	100	2	5029.318
2	Cu	20	V	20	DMAA	4000	1000	100	2	2964.375
2	Fe	5	W	20	DMAA	4000	1000	100	2	4540.673
2	Cu	5	W	20	DMAA	4000	1000	100	2	2848.039
2	Fe	20	W	20	DMAA	4000	1000	100	2	4994.425
2	Cu	20	W	20	DMAA	4000	1000	100	2	3097.556
3	Fe	5	V	5	DMFA	500	1000	120	1	3096.222
3	Cu	5	V	5	DMFA	500	1000	120	1	1130.108
3	Fe	20	V	5	DMFA	500	1000	120	1	3223.721
3	Cu	20	V	5	DMFA	500	1000	120	1	1391.525
3	Fe	5	W	5	DMFA	500	1000	120	1	3367.514
3	Cu	5	W	5	DMFA	500	1000	120	1	735.8303
3	Fe	20	W	5	DMFA	500	1000	120	1	3063.38
3	Cu	20	W	5	DMFA	500	1000	120	1	1264.4
3	Fe	5	V	20	DMFA	500	1000	120	1	3286.707
3	Cu	5	V	20	DMFA	500	1000	120	1	1162.79
3	Fe	20	V	20	DMFA	500	1000	120	1	3153.402

3	Fe	20	W	20	DMFA	4000	1000	120	1	1286.159
3	Cu	20	W	20	DMFA	4000	1000	120	1	3052.865
3	Fe	5	V	5	DMAA	4000	1000	120	1	1140.058
3	Cu	5	V	5	DMAA	4000	1000	120	1	2545.555
3	Fe	20	V	5	DMAA	4000	1000	120	1	1075.588
3	Cu	20	V	5	DMAA	4000	1000	120	1	3170.971
3	Fe	5	W	5	DMAA	4000	1000	120	1	1025.795
3	Cu	5	W	5	DMAA	4000	1000	120	1	3205.365
3	Fe	20	W	5	DMAA	4000	1000	120	1	1144.007
3	Cu	20	W	5	DMAA	4000	1000	120	1	3073.614
3	Fe	5	V	20	DMAA	4000	1000	120	1	991.2687
3	Cu	5	V	20	DMAA	4000	1000	120	1	2875.273
3	Fe	20	V	20	DMAA	4000	1000	120	1	987.423
3	Cu	20	V	20	DMAA	4000	1000	120	1	3169.661
3	Fe	5	W	20	DMAA	4000	1000	120	1	1393.893
3	Cu	5	W	20	DMAA	4000	1000	120	1	3361.081
3	Fe	20	W	20	DMAA	4000	1000	120	1	1464.002
3	Cu	20	W	20	DMAA	4000	1000	120	1	3221.897
4	Fe	5	V	5	DMFA	500	1000	120	2	3562.027
4	Cu	5	V	5	DMFA	500	1000	120	2	1169.025
4	Fe	20	V	5	DMFA	500	1000	120	2	3065.418
4	Cu	20	V	5	DMFA	500	1000	120	2	1179.965
4	Fe	5	W	5	DMFA	500	1000	120	2	3167.984
4	Cu	5	W	5	DMFA	500	1000	120	2	1297.288
4	Fe	20	W	5	DMFA	500	1000	120	2	2967.498
4	Cu	20	W	5	DMFA	500	1000	120	2	502.1629
4	Fe	5	V	20	DMFA	500	1000	120	2	3156.959
4	Cu	5	V	20	DMFA	500	1000	120	2	1254.915
4	Fe	20	V	20	DMFA	500	1000	120	2	3403.2
4	Cu	20	V	20	DMFA	500	1000	120	2	1311.478
4	Fe	5	W	20	DMFA	500	1000	120	2	3215.089
4	Cu	5	W	20	DMFA	500	1000	120	2	801.7368
4	Fe	20	W	20	DMFA	500	1000	120	2	2463.873
4	Cu	20	W	20	DMFA	500	1000	120	2	1286.28
4	Fe	5	V	5	DMAA	500	1000	120	2	3225.547
4	Cu	5	V	5	DMAA	500	1000	120	2	1027.837
4	Fe	20	V	5	DMAA	500	1000	120	2	3455.892
4	Cu	20	V	5	DMAA	500	1000	120	2	1167.907
4	Fe	5	W	5	DMAA	500	1000	120	2	3040.422
4	Cu	5	W	5	DMAA	500	1000	120	2	1625.673
4	Fe	20	W	5	DMAA	500	1000	120	2	2649.228
4	Cu	20	W	5	DMAA	500	1000	120	2	1075.155
4	Fe	5	V	20	DMAA	500	1000	120	2	3454.219
4	Cu	5	V	20	DMAA	500	1000	120	2	1726.461
4	Fe	20	V	20	DMAA	500	1000	120	2	3407.73
4	Cu	20	V	20	DMAA	500	1000	120	2	1391.012
4	Fe	5	W	20	DMAA	500	1000	120	2	3375.964
4	Cu	5	W	20	DMAA	500	1000	120	2	1620.468
4	Fe	20	W	20	DMAA	500	1000	120	2	3347.955
4	Cu	20	W	20	DMAA	500	1000	120	2	1227.624
4	Fe	5	V	5	DMFA	4000	1000	120	2	1285.104
4	Cu	5	V	5	DMFA	4000	1000	120	2	3131.439
4	Fe	20	V	5	DMFA	4000	1000	120	2	1191.938
4	Cu	20	V	5	DMFA	4000	1000	120	2	3019.846
4	Fe	5	W	5	DMFA	4000	1000	120	2	1598.604
4	Cu	5	W	5	DMFA	4000	1000	120	2	3058.827
4	Fe	20	W	5	DMFA	4000	1000	120	2	1111.198
4	Cu	20	W	5	DMFA	4000	1000	120	2	3429.221
4	Fe	5	V	20	DMFA	4000	1000	120	2	1584.459
4	Cu	5	V	20	DMFA	4000	1000	120	2	3624.455
4	Fe	20	V	20	DMFA	4000	1000	120	2	1352.145
4	Cu	20	V	20	DMFA	4000	1000	120	2	3281.384
4	Fe	5	W	20	DMFA	4000	1000	120	2	1323.115
4	Cu	5	W	20	DMFA	4000	1000	120	2	3189.967
4	Fe	20	W	20	DMFA	4000	1000	120	2	1523.089
4	Cu	20	W	20	DMFA	4000	1000	120	2	3211.642
4	Fe	5	V	5	DMAA	4000	1000	120	2	1342.161
4	Cu	5	V	5	DMAA	4000	1000	120	2	3207.565
4	Fe	20	V	5	DMAA	4000	1000	120	2	1494.474
4	Cu	20	V	5	DMAA	4000	1000	120	2	3022.931

5	Cu	20	W	5	DMAA	500	1200	100	1	4260.867
5	Fe	5	V	20	DMAA	500	1200	100	1	1845.083
5	Cu	5	V	20	DMAA	500	1200	100	1	4220.054
5	Fe	20	V	20	DMAA	500	1200	100	1	2422.747
5	Cu	20	V	20	DMAA	500	1200	100	1	4208.349
5	Fe	5	W	20	DMAA	500	1200	100	1	2481.61
5	Cu	5	W	20	DMAA	500	1200	100	1	4414.644
5	Fe	20	W	20	DMAA	500	1200	100	1	2320.681
5	Cu	20	W	20	DMAA	500	1200	100	1	4131.439
5	Fe	5	V	5	DMFA	4000	1200	100	1	3764.029
5	Cu	5	V	5	DMFA	4000	1200	100	1	2456.474
5	Fe	20	V	5	DMFA	4000	1200	100	1	4196.127
5	Cu	20	V	5	DMFA	4000	1200	100	1	2489.818
5	Fe	5	W	5	DMFA	4000	1200	100	1	4326.255
5	Cu	5	W	5	DMFA	4000	1200	100	1	1798.646
5	Fe	20	W	5	DMFA	4000	1200	100	1	4552.989
5	Cu	20	W	5	DMFA	4000	1200	100	1	2438.734
5	Fe	5	V	20	DMFA	4000	1200	100	1	4899.729
5	Cu	5	V	20	DMFA	4000	1200	100	1	1766.201
5	Fe	20	V	20	DMFA	4000	1200	100	1	3853.274
5	Cu	20	V	20	DMFA	4000	1200	100	1	2205.384
5	Fe	5	W	20	DMFA	4000	1200	100	1	4483.398
5	Cu	5	W	20	DMFA	4000	1200	100	1	2193.717
5	Fe	20	W	20	DMFA	4000	1200	100	1	3915.764
5	Cu	20	W	20	DMFA	4000	1200	100	1	2130.307
5	Fe	5	V	5	DMAA	4000	1200	100	1	4268.58
5	Cu	5	V	5	DMAA	4000	1200	100	1	2449.769
5	Fe	20	V	5	DMAA	4000	1200	100	1	4051.658
5	Cu	20	V	5	DMAA	4000	1200	100	1	2319.5
5	Fe	5	W	5	DMAA	4000	1200	100	1	4182.63
5	Cu	5	W	5	DMAA	4000	1200	100	1	1913.637
5	Fe	20	W	5	DMAA	4000	1200	100	1	4171.779
5	Cu	20	W	5	DMAA	4000	1200	100	1	1788.613
6	Fe	5	V	20	DMAA	4000	1200	100	1	4304.112
6	Cu	5	V	20	DMAA	4000	1200	100	1	2340.053
6	Fe	20	V	20	DMAA	4000	1200	100	1	3973.3
6	Cu	20	V	20	DMAA	4000	1200	100	1	2242.964
6	Fe	5	W	20	DMAA	4000	1200	100	1	4220.131
6	Cu	5	W	20	DMAA	4000	1200	100	1	2029.409
6	Fe	20	W	20	DMAA	4000	1200	100	1	4474.279
6	Cu	20	W	20	DMAA	4000	1200	100	1	2185.812
6	Fe	5	V	5	DMFA	500	1200	100	2	3200.736
6	Cu	5	V	5	DMFA	500	1200	100	2	5251.12
6	Fe	20	V	5	DMFA	500	1200	100	2	2941.772
6	Cu	20	V	5	DMFA	500	1200	100	2	5348.456
6	Fe	5	W	5	DMFA	500	1200	100	2	3216.89
6	Cu	5	W	5	DMFA	500	1200	100	2	5601.562
6	Fe	20	W	5	DMFA	500	1200	100	2	3213.059
6	Cu	20	W	5	DMFA	500	1200	100	2	5455.892
6	Fe	5	V	20	DMFA	500	1200	100	2	3248.214
6	Cu	5	V	20	DMFA	500	1200	100	2	4972.636
6	Fe	20	V	20	DMFA	500	1200	100	2	3355.542
6	Cu	20	V	20	DMFA	500	1200	100	2	5019.747
6	Fe	5	W	20	DMFA	500	1200	100	2	3747.147
6	Cu	5	W	20	DMFA	500	1200	100	2	5053.546
6	Fe	20	W	20	DMFA	500	1200	100	2	3082.532
6	Cu	20	W	20	DMFA	500	1200	100	2	5055.11
6	Fe	5	V	5	DMAA	500	1200	100	2	2903.681
6	Cu	5	V	5	DMAA	500	1200	100	2	4726.624
6	Fe	20	V	5	DMAA	500	1200	100	2	3378.448
6	Cu	20	V	5	DMAA	500	1200	100	2	5179.236
6	Fe	5	W	5	DMAA	500	1200	100	2	3013.919
6	Cu	5	W	5	DMAA	500	1200	100	2	4803.361
6	Fe	20	W	5	DMAA	500	1200	100	2	3213.767
6	Cu	20	W	5	DMAA	500	1200	100	2	5545.379
6	Fe	5	V	20	DMAA	500	1200	100	2	3585.461
6	Cu	5	V	20	DMAA	500	1200	100	2	4672.836
6	Fe	20	V	20	DMAA	500	1200	100	2	3238.526
6	Cu	20	V	20	DMAA	500	1200	100	2	5161.146
6	Fe	5	W	20	DMAA	500	1200	100	2	3014.8

7	Cu	20	V	5	DMFA	4000	1200	120	1	3393.315
7	Fe	5	W	5	DMFA	4000	1200	120	1	1403.261
7	Cu	5	W	5	DMFA	4000	1200	120	1	3555.009
7	Fe	20	W	5	DMFA	4000	1200	120	1	1308.279
7	Cu	20	W	5	DMFA	4000	1200	120	1	3512.98
7	Fe	5	V	20	DMFA	4000	1200	120	1	1284.812
7	Cu	5	V	20	DMFA	4000	1200	120	1	3435.316
7	Fe	20	V	20	DMFA	4000	1200	120	1	1694.665
7	Cu	20	V	20	DMFA	4000	1200	120	1	3496.463
7	Fe	5	W	20	DMFA	4000	1200	120	1	1143.947
7	Cu	5	W	20	DMFA	4000	1200	120	1	3456.876
7	Fe	20	W	20	DMFA	4000	1200	120	1	1617.505
7	Cu	20	W	20	DMFA	4000	1200	120	1	3879.49
7	Fe	5	V	5	DMAA	4000	1200	120	1	1273.745
7	Cu	5	V	5	DMAA	4000	1200	120	1	3382.074
7	Fe	20	V	5	DMAA	4000	1200	120	1	881.0287
7	Cu	20	V	5	DMAA	4000	1200	120	1	3104.413
7	Fe	5	W	5	DMAA	4000	1200	120	1	1395.572
7	Cu	5	W	5	DMAA	4000	1200	120	1	3141.805
7	Fe	20	W	5	DMAA	4000	1200	120	1	1774.357
7	Cu	20	W	5	DMAA	4000	1200	120	1	3413.901
8	Fe	5	V	20	DMAA	4000	1200	120	1	1649.139
8	Cu	5	V	20	DMAA	4000	1200	120	1	3368.794
8	Fe	20	V	20	DMAA	4000	1200	120	1	1824.133
8	Cu	20	V	20	DMAA	4000	1200	120	1	3660.883
8	Fe	5	W	20	DMAA	4000	1200	120	1	1179.379
8	Cu	5	W	20	DMAA	4000	1200	120	1	3628.204
8	Fe	20	W	20	DMAA	4000	1200	120	1	1293.674
8	Cu	20	W	20	DMAA	4000	1200	120	1	3019.058
8	Fe	5	V	5	DMFA	500	1200	120	2	2990.086
8	Cu	5	V	5	DMFA	500	1200	120	2	1029.93
8	Fe	20	V	5	DMFA	500	1200	120	2	3062.541
8	Cu	20	V	5	DMFA	500	1200	120	2	1242.527
8	Fe	5	W	5	DMFA	500	1200	120	2	3147.093
8	Cu	5	W	5	DMFA	500	1200	120	2	1316.01
8	Fe	20	W	5	DMFA	500	1200	120	2	3127.044
8	Cu	20	W	5	DMFA	500	1200	120	2	1729.955
8	Fe	5	V	20	DMFA	500	1200	120	2	3923.339
8	Cu	5	V	20	DMFA	500	1200	120	2	1251.202
8	Fe	20	V	20	DMFA	500	1200	120	2	3291.114
8	Cu	20	V	20	DMFA	500	1200	120	2	1309.178
8	Fe	5	W	20	DMFA	500	1200	120	2	3166.405
8	Cu	5	W	20	DMFA	500	1200	120	2	1079.929
8	Fe	20	W	20	DMFA	500	1200	120	2	3399.78
8	Cu	20	W	20	DMFA	500	1200	120	2	1317.061
8	Fe	5	V	5	DMAA	500	1200	120	2	3249.165
8	Cu	5	V	5	DMAA	500	1200	120	2	1310.566
8	Fe	20	V	5	DMAA	500	1200	120	2	3181.768
8	Cu	20	V	5	DMAA	500	1200	120	2	1384.317
8	Fe	5	W	5	DMAA	500	1200	120	2	3483.545
8	Cu	5	W	5	DMAA	500	1200	120	2	1483.464
8	Fe	20	W	5	DMAA	500	1200	120	2	3243.016
8	Cu	20	W	5	DMAA	500	1200	120	2	1659.831
8	Fe	5	V	20	DMAA	500	1200	120	2	3832.087
8	Cu	5	V	20	DMAA	500	1200	120	2	1434.119
8	Fe	20	V	20	DMAA	500	1200	120	2	3898.378
8	Cu	20	V	20	DMAA	500	1200	120	2	1514.125
8	Fe	5	W	20	DMAA	500	1200	120	2	3320.126
8	Cu	5	W	20	DMAA	500	1200	120	2	1269.161
8	Fe	20	W	20	DMAA	500	1200	120	2	3552.422
8	Cu	20	W	20	DMAA	500	1200	120	2	1408.177
8	Fe	5	V	5	DMFA	4000	1200	120	2	1330.367
8	Cu	5	V	5	DMFA	4000	1200	120	2	3233.872
8	Fe	20	V	5	DMFA	4000	1200	120	2	1119.671
8	Cu	20	V	5	DMFA	4000	1200	120	2	3565.294
8	Fe	5	W	5	DMFA	4000	1200	120	2	1540.59
8	Cu	5	W	5	DMFA	4000	1200	120	2	3197.359
8	Fe	20	W	5	DMFA	4000	1200	120	2	1421.148
8	Cu	20	W	5	DMFA	4000	1200	120	2	3467.429
8	Fe	5	V	20	DMFA	4000	1200	120	2	1265.396

In this iteration, each of the metal acetylacetonates, the DMAA, and the DMFA is made up as a stock solution in phenol. An appropriate quantity of each stock solution is then combined using a Hamilton MicroLab 4000 laboratory robot into a single vial for mixing. For example, the stock solutions to produce rows 1, 65, 129,193, 257, 321, 385, and 449 or TABLE 12, are 0.01 molar Pd(acetylacetonate), 0.01 molar each of Fe(acetylacetonate) and V(acetylacetonate) and 5 molar DMFA. Ten ml of each stock solution is produced by manual weighing and mixing. Aliquots of the stock solutions are measured as follows in TABLE 13. The mixture is stirred using a miniature magnetic stirrer.

TABLE 13

0.01 molar Pd(acetylacetonate)	25 microliters
0.01 molar Fe(acetylacetonate)	125 microliters
0.01 molar V(acetylacetonate)	125 microliters
5 molar DMFA	25 microliters
Pure Phenol	700 microliters

In the second iteration, pressure chamber reactor 54 is heated and pressurized to the conditions shown as Block 1 in TABLE 7. The procedure described as iteration 1 is repeated in the system described with reference to FIG 3 and FIG. 4 with the species of TABLE 10. This process is repeated until all the block conditions have been run.

The performance of each vial is given in the column "TON" of TABLE 13. These results are then analyzed using a "General Linear Model" (GLM) routine in Minitab software. A GLM routine performs analysis of variance (ANOVA) on any specified mathematical model potentially describing a relationship between control factors and response. The routine determines which terms of the model actually have a statistically significant influence on response. The GLM routine is set to calculate an Analysis of Variance (ANOVA) for all main effects, 2-way interactions, and 3-way interactions in data. In a factorial design, an effect of a factor is the average change in response when the value of that factor is changed from its low level to its high level. The effect is a main effect when it is calculated without including the influence of other factors. A 2-way interaction mathematically describes change in the effect of one factor when a second factor is changed from its low level to its high level. A 3-way interaction mathematically describes change in the effect of one factor when two other factors simultaneously are changed from respective low levels to respective high levels.

The ANOVA in this Example is given in TABLE 14.

TABLE 14

Pressure*CS	1	11954	11954	11954	0.146	0.702	
Temperature*Time	1	33291520	33291520	33291520	407.672	0.000	YES
Temperature*M1	1	43430	43430	43430	0.532	0.466	
Temperature*M2	1	94767	94767	94767	1.160	0.282	
Temperature*CS	1	90412	90412	90412	1.107	0.293	
Time*M1	1	1491	1491	1491	0.018	0.893	
Time*M2	1	93605	93605	93605	1.146	0.285	
Time*CS	1	76043	76043	76043	0.931	0.335	
M1*M2	1	77799	77799	77799	0.953	0.330	
M1*CS	1	169760	169760	169760	2.079	0.150	
M2*CS	1	407136	407136	407136	4.986	0.026	
M1 amt*M2 amt*CS amt	1	361079	361079	361079	4.422	0.036	
M1 amt*M2 amt*Pressure	1	21432	21432	21432	0.262	0.609	
M1 amt*M2 amt*Temperature	1	271	271	271	0.003	0.954	
M1 amt*M2 amt*Time	1	13991	13991	13991	0.171	0.679	
M1 amt*M2 amt*M1	1	281433	281433	281433	3.446	0.064	
M1 amt*M2 amt*M2	1	1	1	1	0.000	0.997	
M1 amt*M2 amt*CS	1	116073	116073	116073	1.421	0.234	
M1 amt*CS amt*Pressure	1	114627	114627	114627	1.404	0.237	
M1 amt*CS amt*Temperature	1	466	466	466	0.006	0.940	
M1 amt*CS amt*Time	1	69157	69157	69157	0.847	0.358	
M1 amt*CS amt*M1	1	164860	164860	164860	2.019	0.156	
M1 amt*CS amt*M2	1	14698	14698	14698	0.180	0.672	
M1 amt*CS amt*CS	1	334131	334131	334131	4.092	0.044	
M1 amt*Pressure*Temperature	1	235	235	235	0.003	0.957	
M1 amt*Pressure*Time	1	167809	167809	167809	2.055	0.153	
M1 amt*Pressure*M1	1	8172	8172	8172	0.100	0.752	
M1 amt*Pressure*M2	1	4377	4377	4377	0.054	0.817	
M1 amt*Pressure*CS	1	6356	6356	6356	0.078	0.780	
M1 amt*Temperature*Time	1	67161	67161	67161	0.822	0.365	
M1 amt*Temperature*M1	1	194664	194664	194664	2.384	0.123	
M1 amt*Temperature*M2	1	569	569	569	0.007	0.934	
M1 amt*Temperature*CS	1	11	11	11	0.000	0.991	
M1 amt*Time*M1	1	6489	6489	6489	0.079	0.778	
M1 amt*Time*M2	1	30862	30862	30862	0.378	0.539	

Source	DF	Seq SS	Adj SS	Adj MS	F Ratio	P	Significant at P<0.01
M1 amt	1	16412	16412	16412	0.201	0.654	
M2 amt	1	77926	77926	77926	0.954	0.329	
CS amt	1	33586	33586	33586	0.411	0.522	
Pressure	1	4616039	4616039	4616039	56.526	0.000	YES
Temperature	1	216802139	216802139	216802139	2654.854	0.000	YES
Time	1	31205785	31205785	31205785	382.131	0.000	YES
M1	1	22404811	22404811	22404811	274.358	0.000	YES
M2	1	182205	182205	182205	2.231	0.136	
CS	1	3702	3702	3702	0.045	0.832	
M1 amt*M2 amt	1	27036	27036	27036	0.331	0.565	
M1 amt*CS amt	1	58292	58292	58292	0.714	0.399	
M1 amt*Pressure	1	61467	61467	61467	0.753	0.386	
M1 amt*Temperature	1	26926	26926	26926	0.330	0.566	
M1 amt*Time	1	110415	110415	110415	1.352	0.246	
M1 amt*M1	1	34335	34335	34335	0.420	0.517	
M1 amt*M2	1	232680	232680	232680	2.849	0.092	
M1 amt*CS	1	260446	260446	260446	3.189	0.075	
M2 amt*CS amt	1	79627	79627	79627	0.975	0.324	
M2 amt*Pressure	1	341447	341447	341447	4.181	0.042	
M2 amt*Temperature	1	477	477	477	0.006	0.939	
M2 amt*Time	1	125869	125869	125869	1.541	0.215	
M2 amt*M1	1	14190	14190	14190	0.174	0.677	
M2 amt*M2	1	81553	81553	81553	0.999	0.318	
M2 amt*CS	1	8125	8125	8125	0.099	0.753	
CS amt*Pressure	1	33749	33749	33749	0.413	0.521	
CS amt*Temperature	1	295416	295416	295416	3.618	0.058	
CS amt*Time	1	7438	7438	7438	0.091	0.763	
CS amt*M1	1	132568	132568	132568	1.623	0.203	
CS amt*M2	1	37280	37280	37280	0.457	0.500	
CS amt*CS	1	23702	23702	23702	0.290	0.590	
Pressure*Temperature	1	40272	40272	40272	0.493	0.483	
Pressure*Time	1	38	38	38	0.000	0.983	
Pressure*M1	1	253770	253770	253770	3.108	0.079	
Pressure*M2	1	260899	260899	260899	3.195	0.075	
M1 amt*Time*CS	1	163612	163612	163612	2.004	0.158	
M1 amt*M1*M2	1	77397	77397	77397	0.948	0.331	
M1 amt*M1*CS	1	11421	11421	11421	0.140	0.709	
M1 amt*M2*CS	1	59409	59409	59409	0.727	0.394	
M2 amt*CS amt*Pressure	1	6344	6344	6344	0.078	0.781	
M2 amt*CS amt*Temperature	1	0	0	0	0.000	1.000	
M2 amt*CS amt*Time	1	70019	70019	70019	0.857	0.355	
M2 amt*CS amt*M1	1	89887	89887	89887	1.101	0.295	
M2 amt*CS amt*M2	1	120523	120523	120523	1.476	0.225	
M2 amt*CS amt*CS	1	8479	8479	8479	0.104	0.747	
M2 amt*Pressure*Temperature	1	190090	190090	190090	2.328	0.128	
M2 amt*Pressure*Time	1	14716	14716	14716	0.180	0.671	
M2 amt*Pressure*M1	1	7373	7373	7373	0.090	0.764	
M2 amt*Pressure*M2	1	16357	16357	16357	0.200	0.655	
M2 amt*Pressure*CS	1	35027	35027	35027	0.429	0.513	
M2 amt*Temperature*Time	1	26831	26831	26831	0.329	0.567	
M2 amt*Temperature*M1	1	626	626	626	0.008	0.930	
M2 amt*Temperature*M2	1	94448	94448	94448	1.157	0.283	
M2 amt*Temperature*CS	1	1212	1212	1212	0.015	0.903	
M2 amt*Time*M1	1	77055	77055	77055	0.944	0.332	
M2 amt*Time*M2	1	6233	6233	6233	0.076	0.782	
M2 amt*Time*CS	1	337817	337817	337817	4.137	0.043	
M2 amt*M1*M2	1	38653	38653	38653	0.473	0.492	
M2 amt*M1*CS	1	23751	23751	23751	0.291	0.590	
M2 amt*M2*CS	1	3270	3270	3270	0.040	0.842	
CS amt*Pressure*Temperature	1	84561	84561	84561	1.035	0.310	
CS amt*Pressure*Time	1	212868	212868	212868	2.607	0.107	
CS amt*Pressure*M1	1	34495	34495	34495	0.422	0.516	
CS amt*Pressure*M2	1	20299	20299	20299	0.249	0.618	
CS amt*Pressure*CS	1	12034	12034	12034	0.147	0.701	
CS amt*Temperature*Time	1	174636	174636	174636	2.139	0.144	
CS amt*Temperature*M1	1	535239896	535239896	535239896	6554.288	0.000	YES
CS amt*Temperature*M2	1	4708	4708	4708	0.058	0.810	
CS amt*Temperature*CS	1	331	331	331	0.004	0.949	
CS amt*Time*M1	1	112874	112874	112874	1.382	0.240	

CS amt*Time*M2	1	1469	1469	1469	0.018	0.893	
CS amt*Time*CS	1	804	804	804	0.010	0.921	
CS amt*M1*M2	1	75785	75785	75785	0.928	0.336	
CS amt*M1*CS	1	22036	22036	22036	0.270	0.604	
CS amt*M2*CS	1	34743	34743	34743	0.425	0.515	
Pressure*Temperature*Time	1	950930	950930	950930	11.645	0.001	YES
Pressure*Temperature*M1	1	18226	18226	18226	0.223	0.637	
Pressure*Temperature*M2	1	11544	11544	11544	0.141	0.707	
Pressure*Temperature*CS	1	67428	67428	67428	0.826	0.364	
Pressure*Time*M1	1	310071	310071	310071	3.797	0.052	
Pressure*Time*M2	1	10784	10784	10784	0.132	0.717	
Pressure*Time*CS	1	2008	2008	2008	0.025	0.875	
Pressure*M1*M2	1	12343	12343	12343	0.151	0.698	
Pressure*M1*CS	1	14220	14220	14220	0.174	0.677	
Pressure*M2*CS	1	67936	67936	67936	0.832	0.362	
Temperature*Time*M1	1	221695	221695	221695	2.715	0.100	
Temperature*Time*M2	1	38	38	38	0.000	0.983	
Temperature*Time*CS	1	10	10	10	0.000	0.991	
Temperature*M1*M2	1	24040	24040	24040	0.294	0.588	
Temperature*M1*CS	1	257092	257092	257092	3.148	0.077	
Temperature*M2*CS	1	848	848	848	0.010	0.919	
Time*M1*M2	1	53303	53303	53303	0.653	0.420	
Time*M1*CS	1	44080	44080	44080	0.540	0.463	
Time*M2*CS	1	7295	7295	7295	0.089	0.765	
M1*M2*CS	1	319669	319669	319669	3.915	0.049	
Error	382	31195094	31195094	81662.55			
Total	511	885328201					

The column "Significant at P<0.01 " of TABLE 14 defines the factors and interactions in the model, which have a statistically significant effect on the response with a probability of incorrect decision of less than 1%. The column shows that only 5 of the 129 possible main effects, 2-way interactions, and 3-way interactions have a significant effect on the TON. It is noted that a 3-way interaction (CS amt*Temperature*M1) has the largest influence on the TON (FIG.5).

This Example shows that the disclosed method can perform large numbers of experiments and can sort out variables in a combinatorial experiment to detect key process interactions. From this interaction a favorable condition for obtaining high (>5500) TON is determined as shown in TABLE 15.

TABLE 15

Factor	Identity	Amount
M1	Cu	Any
M2	Any	Any
CS	Any	500
Pressure		Any
Temperature		100C
Time		2 hr

:

The interaction identifies a unique condition in which two formulation variables (M1 = Cu and CS amount = 500) generate a very high level of TON only when the temperature is at 100°C.

It will be understood that each of the elements described above, or two or more together, may also find utility in applications differing from the types described herein. While the invention has been illustrated and described as embodied in a sequential high-throughput screening method and system, it is not intended to be limited to the details shown, since various modifications and substitutions can be made without departing in any way from the spirit of the present invention. For example, robotic equipment can be used to prepare samples and various types of parallel analytical screening methods can be incorporated. As such, further modifications and equivalents of the invention herein disclosed may occur to persons skilled in the art using no more than routine experimentation, and all such modifications and equivalents are believed to be within the spirit and scope of the invention as defined by the following claims.